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Stroke. Author manuscript; available in PMC 2008 November 03.

Published in final edited form as:
Stroke. 2006 February ; 37(2): 364–370. doi:10.1161/01.STR.0000199065.12908.62.

Does *Apolipoprotein E Genotype* Influence the Risk of Ischemic Stroke, Intracerebral Hemorrhage, or Subarachnoid Hemorrhage?:

Systematic Review and Meta-Analyses of 31 Studies Among 5961 Cases and 17 965 Controls

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Abstract

Background and Purpose—*Apolipoprotein E genotype* (*APOE*) is associated with cholesterol metabolism, ischemic heart disease, and cerebral amyloid angiopathy, and so may affect risk of both ischemic and hemorrhagic stroke.

Methods—We comprehensively sought and identified studies of the association of apoE with ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). We did meta-analyses to assess the evidence for an association between *APOE* and the various pathological types and subtypes of stroke, and assessed the effects of several methodological criteria.

Results—We analyzed data from 31 eligible studies (26 IS, 8 ICH, and 3 SAH) in 5961 cases and 17 965 controls. ∈4 allele-containing (∈4+) genotypes were significantly associated with IS (odds ratio [OR], 1.11; 95% CI, 1.01 to 1.22) and SAH (OR, 1.42; 95% CI, 1.01 to 1.99) and nonsignificantly with ICH (OR, 1.16; 95% CI, 0.93 to 1.44), whereas ∈2+ genotypes were associated with ICH (OR, 1.32; 95% CI, 1.01 to 1.74). Associations appeared stronger with ∈4+ genotypes for large artery compared with other IS subtypes and for Asian compared with white populations, and with ∈2+ genotypes for lobar compared with deep hemorrhages. However, we found no association between ∈4+ genotypes and IS when we analyzed only larger studies (>200 cases; OR, 0.99; 95% CI, 0.88 to 1.11) or studies without control selection bias (OR, 0.99; 95% CI, 0.85 to 1.17).

Conclusions—Publication and selection biases make existing studies of *APOE* and stroke unreliable. Further, very large, methodologically rigorous studies are needed.

Keywords

apolipoproteins E; genetics; meta-analysis; stroke

Twin and family history studies suggest a genetic component to the risk of all 3 main pathological types of stroke (ischemic stroke [IS], intracerebral hemorrhage [ICH], and

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subarachnoid hemorrhage [SAH]).1-4 Genes influencing stroke risk may act through the modification of known risk factors (such as hypertension)5,6 or through novel pathways.

Studies investigating genetic risk factors for human stroke have generally taken a candidate gene case-control approach, studying polymorphisms, the functional consequences of which make them likely to influence stroke risk.7,8 Because stroke is complex and pathologically heterogeneous, there are a large number of potential candidate genes (eg, those involved in coagulation, cholesterol metabolism, and blood pressure regulation).7,8 The relative risk associated with any candidate gene is therefore likely to be small, probably not >1.5 at most, meaning that candidate gene studies in stroke, as for ischemic heart disease, need several thousand cases and controls to be able to identify reliably any real associations.9,10 Studying several candidate genes or comparing genetic influences between stroke subtypes or other subgroups needs even larger numbers.11 Many candidate gene studies in stroke have been completed, but they have generally been too small to reach reliable conclusions, and many have had other methodological shortcomings, for example, in the selection of an appropriate control group.7,8,12

The *apolipoprotein E gene* (apoE for protein, *APOE* for gene) is one of the most widely studied genes in vascular and neurodegenerative diseases.13 Its protein product, apoE, is a glycoprotein with 3 common isoforms, E2, E3, and E4, encoded by the alleles ϵ2, ϵ3, and ϵ4, giving rise to 6 genotypes, with the genotype ϵ3/ϵ3 occurring in about one half to two thirds of people in most populations. The protein plays a major role in lipid transport and metabolism and is also significantly expressed in brain.

Compared with ϵ3/ϵ3, ϵ4 allele-containing (ϵ4+) genotypes are associated with increased total cholesterol levels, whereas ϵ2 allele-containing (ϵ2+) genotypes are associated with decreased levels.13 This may partly explain why ϵ4 carriers have an increased risk of ischemic heart disease and the observed association in some studies with markers of atherosclerosis (eg, carotid intima-media thickness).14,15 These associations might suggest that ϵ4 carriers should be at increased risk of IS, particularly large artery atherothrombotic stroke. However, studies of *APOE* and IS have produced conflicting results.7,8,16

Studies of cerebral vascular pathology in human brain autopsy and biopsy specimens have suggested that *APOE* influences cerebral amyloid angiopathy, which is thought to account for a substantial proportion of lobar ICHs in the elderly. It appears that although the ϵ4 allele enhances amyloid deposition in blood vessels, the ϵ2 allele predisposes to vasculopathic changes leading to rupture of amyloid laden vessels.17,18 Thus, one might expect ϵ4 and ϵ2 carriers to have increased susceptibility to ICH, especially in a lobar location.

A few studies have published data on *APOE* and SAH. Although variation in susceptibility to vasculopathic changes could conceivably explain an association, we are not aware of any evidence for this.

In this article, we use systematic review and meta-analysis methods to assess the potential association between *APOE* and the various pathological types and subtypes of stroke.

Methods

Study Identification and Inclusion/Exclusion Criteria

We sought all available published studies in which the association between *APOE* and clinically evident (ie, not diagnosed on brain imaging or autopsy only) IS, ICH, or SAH had been studied in adult humans. We used a detailed electronic search strategy in Medline and

Embase from 1966 to the end of October 2004, including a combination of MeSH terms and text words for apoE and for stroke and its subtypes (see Appendix), checked the reference lists of all relevant studies and review articles thus identified, and also checked the relevant chapters of recently published textbooks on stroke or stroke genetics.

We excluded studies in which all types of stroke were studied together with no distinction between different pathological types. We also excluded studies of recurrent stroke in patients with a previous stroke, or of stroke in patients with serious disease. We initially sought both full articles and abstracts in all languages, but later excluded studies published in abstract form only and several studies in non-English languages for which translations were not readily available because these were all very small and their inclusion would not have materially affected our conclusions (see Results). For each of the 3 main pathological types of stroke (IS, ICH, and SAH), 2 authors independently selected studies fulfilling our inclusion criteria, resolving disagreements by discussion.

Data Extraction

For each study selected, we extracted information on: year of publication; study design (eg, case control, case cohort, cross-sectional); country in which the study was conducted; ethnicity of the subjects studied; the number, source, and definitions of the cases and controls; case-control matching variables, if any; mean age and percentage male among cases and controls; reported presence of Hardy-Weinberg equilibrium among cases and controls; whether genotyping staff were blind to case-control status; the types of samples genotyped and genotyping method used; and availability of genotype or allele frequency data for subtypes of IS or ICH. We also extracted data on the numbers of cases and controls with each of the 6 *APOE* genotypes, allowing calculation of numbers with ϵ4 allele-containing and ϵ2 allele-containing genotypes as well as of ϵ4 and ϵ2 allele frequencies among case and control chromosomes. For a few studies, we were only able to extract data on allele frequencies.

For studies with >1 publication describing results among the same or overlapping groups of patients or controls, we included only the largest of the available published data sets to avoid double counting. For studies with >1 control group, we used the most appropriate control group according to the methodological criteria outlined below, and where neither control group was methodologically superior, we used the largest.

At least 2 authors extracted the above information from each study, resolving any disagreements by discussion.

Statistical Analyses

We used Cochrane RevMan (version 4.2) software.19 For each study, we calculated an unadjusted ratio of the odds of being a case to the odds of being a control given an ϵ4+ genotype, and given an ϵ2+ genotype. For each study, we also extracted information (where available) on the corresponding adjusted odds ratio (OR) that took account of any matching or other potential confounding variables. We calculated pooled ORs from the unadjusted data using the Mantel-Haenszel method.20

We did several prespecified subgroup analyses. For IS, we assessed the effects on the results of ethnicity and of different IS subtypes, and for ICH we assessed the effects of lobar versus deep hemorrhage locations. For IS, where the total number of studies and subjects was large, we also assessed the effects of several methodological quality criteria: the potential for small study bias (particularly publication bias), comparing results for studies with ≥200 cases versus those with <200 cases; the quality of selection of the controls, comparing results for studies in which controls were selected concurrently and without potential bias from the

same population as the cases (so that if a control in the study had had a stroke they would have been a case) versus those in which they were not (or where insufficient information was given); blinding of genotyping staff; and genotyping method.

For our primary analyses, we used the fixed-effects method of meta-analysis, but we also checked the effects of repeating all analyses using a random-effects model. Our primary analyses were based on genotypes, avoiding the need to assume presence of Hardy-Weinberg equilibrium in cases and controls, but we also did analyses comparing ϵ4 and ϵ2 allele frequencies between case and control chromosomes.

Results

From 866 articles identified, we selected 42 potentially relevant studies after perusal of all titles, abstracts and, where necessary, full articles.2,17,[w1-w44] After exclusions, we were left with a total of 31 studies in 5961 cases and 17 965 controls (Figure 1).

APOE and *IS*

We included 26 studies (5018 cases and 16 921 controls; see Figure 1 and details of study characteristics in the supplemental Table I, available online at http://stroke.ahajournals.org). The studies were conducted in several European countries, the United States, Brazil, Taiwan, China, Japan, Korea, and Bangladesh, and included populations of varying ethnicity. Most used a retrospective case-control design, but a few identified cases and controls within a cohort. The studies were generally small (mean number of cases 193; only 11 included >200 cases, and none included >1000 cases). Only 4 (1 retrospective case-control study, and 3 conducted within cohorts) described the selection of the controls according to our methodological ideal (see above).[w7,w13,w15,w18] Although several studies matched controls to cases on age, sex, and occasionally other variables, and most collected information on potentially confounding stroke risk factors, only a few performed an appropriate analysis accounting for these variables.[w2,w4,w7,w11,w12,w15,w16,w18,w24] Only 10 studies checked for and reported on Hardy-Weinberg equilibrium,[w6,w9,w13-15,w18,w20,w21,w23,w25,w26] and only 7 mentioned blinding of genotyping staff.[w10,w11,w13,w15,w20,w21,w26,w27] Most carried out genotyping on blood samples, using polymerase chain reaction (PCR) and restriction enzyme digestion methods, whereas a few used the Taqman fluorescent detection system and several assigned *APOE* genotypes from apoE phenotypes, obtained by isoelectric focusing and immunoblotting. Two studies provided data on allele frequencies but not genotypes.[w6,w20,w21] Only 7 studies provided data on genotypes for ≥1 etiological subtypes of IS (large artery IS, small artery or lacunar IS, cardioembolic stroke, and others; Figure 1; supplemental Table I).[w1,w5,w12,w16,w17,w22,w24]

Figure 2 shows ORs for ϵ4+ versus ϵ4- genotypes for the 24 studies with genotype data, separately and overall. The pooled OR suggested a slight excess risk of IS for ϵ4+ genotypes (OR, 1.11; 95% CI, 1.01 to 1.22) but with marginal statistical significance (P=0.03), a wide CI, and substantial heterogeneity between the results of the studies ($\chi^2$23df=75.4; P<0.00001). When we looked separately at the different IS subtypes in the 7 studies with available data, there appeared to be a stronger (albeit not independently significant) relationship between ϵ4+ genotypes and large artery ISs (OR, 1.33; 95% CI, 0.99 to 1.78), with no clear evidence of an association with small artery (lacunar), cardioembolic, or other/unknown IS subtypes (Figure 3). Analyses by ethnic group suggested a stronger relationship between ϵ4+ genotypes and IS in the various Asian populations than in whites or others, with marginally significant heterogeneity between the ethnic groups (Figure 3). However, when we restricted analyses to larger studies with ≥200 cases (which are less prone to small study biases, especially publication bias) or to studies with unbiased, methodologically

"ideal" control groups, the modest overall association between ϵ4+ genotypes and IS disappeared (OR larger studies, 0.99, 95% CI, 0.88 to 1.11; OR "ideal" controls, 0.99, 95% CI, 0.85 to 1.17; Figure 3). Blinding of genotyping staff and the genotyping method used appeared not to influence the results much (Figure 3). The effect of study size also influenced the ethnicity subgroup results because the presence of an effect of ϵ4+ genotypes on IS in Asian ethnic groups was only present in the studies with <200 cases (OR smaller studies, 2.17, 95%, CI 1.56 to 3.03; OR larger studies, 1.09, 95% CI, 0.88 to 1.35; heterogeneity between 2 groups of studies $\chi^2$1df=11.6; P=0.0007). We found no overall association between ϵ2+ genotypes and IS (OR, 0.99; 95% CI, 0.87 to 1.13).

Only a few studies reported both unadjusted and appropriately adjusted ORs, but of those that did, there was generally little difference between the 2 results,[w7,w11,w12,w15,w16,w18,w25] suggesting that our meta-analysis of data that did not account for matching or take account of potential confounders was reasonable.

APOE and *ICH*

Eight studies (706 cases and 2526 controls) were included (see Figure 1 and details in the supplemental Table I). 2,17,[w6,w12,w13,w16,w28-w33] They were conducted in the United Kingdom, Portugal, the United States, Japan, and Bangladesh. All used a retrospective case-control design, and only 1 described selecting controls according to our methodological ideal.[w13] The studies were mainly conducted in single centers and so were small, with the number of cases ranging from 38 to 188. Four matched cases and controls on age and sex, 4 checked for and reported on Hardy-Weinberg equilibrium, 3 mentioned blinding of genotyping staff, and all used PCR and restriction enzyme digestion methods for genotyping (supplemental Table I). Two studies provided data on allele frequencies but not genotypes. 17,[w6,w28,w29] Four studies provided data separately for lobar and deep ICHs but 1 of these provided allele frequency data only.2,17,[w28-w32]

There was a marginally significant increased odds of ICH among those with an ϵ2+ genotype (OR, 1.32; 95% CI, 1.01 to 1.74; Figure 4a). Analyses by hemorrhage location suggested a stronger relationship for lobar than for deep hemorrhage (Figure 4b). There was a nonsignificant trend toward increased odds of ICH among those with an ϵ4+ genotype (OR, 1.16; 95% CI, 0.93 to 1.44; Figure 5a), and the suggestion of a stronger (but still nonsignificant) relationship for lobar than for deep hemorrhage (Figure 5b). For 2 studies, we were able to compare unadjusted ORs with appropriately adjusted ORs accounting for matching and potentially confounding variables and found these to be very similar.2,[w12]

APOE and *SAH*

Three studies (237 cases and 1655 controls) were included (Figure 1; supplemental Table I).[w12,w31,w33] Pooled analyses showed marginally significant increased odds of SAH in ϵ4 carriers (OR, 1.42; 95% CI, 1.01 to 1.99) but no association with ϵ2+ genotypes (OR, 1.14; 95% CI, 0.75 to 1.76).

For all of our analyses, random-effects and allele frequency-based analyses generated similar results (data not shown).

Discussion

The relationship between *APOE* and IS has been studied in large numbers of subjects in case-control studies, but the individual studies were generally small and had a variety of other methodological limitations. In our systematic review, overall pooled results suggested an association between ϵ4+ genotypes and IS, particularly in large artery IS and in Asians, but analyses of methodological quality criteria showed that these results could have arisen

from small study and control selection biases. The association between ∈4+ genotypes and IS disappeared when we considered only the larger (≥200 cases) studies or only the few studies with "ideal," unbiased selection of controls (although the heterogeneity between studies with "ideal" and "nonideal" controls was not statistically significant at conventional levels). The most important small study bias is probably publication bias (ie, the results of small negative studies are far less likely to be published than those of small positive studies).21 Other methodological characteristics of the studies (such as blinding of genotyping staff and genotyping method) seemed to have less influence on whether or not an association was detected. Thus, despite evidence of a moderate-sized association between ∈4+ genotypes and ischemic heart disease (OR, ≈1.3),14 there is currently no convincing evidence for an association with IS. An association, particularly with large artery IS, remains possible, but the small numbers of studies and subjects with information on ischemic subtypes and other methodological limitations preclude firm conclusions.

Our overall results for ICH showed a significant association with ∈2+ genotypes (or the ∈2 allele), a trend toward an association with ∈4+ genotypes (or the ∈4 allele), and a strengthening of these associations for lobar hemorrhages. This would appear to support the findings of studies of cerebral amyloid angiopathy, but all of the ICH studies were small, control group selection was generally of doubtful quality, and reporting bias may have affected the results for lobar versus deep hemorrhage because they were based on 3 of the 4 most positive studies. The results are therefore no more than suggestive.

Despite no published theoretical basis for an association between *APOE* and SAH, we found a just statistically significant association with ∈4+ genotypes in our meta-analysis. However, this was based on only small numbers of cases and controls, and seems far more likely to be the combined result of publication and reporting bias than to reflect a true underlying association.

None of the studies in our systematic review even approached fulfilling a set of recently suggested methodological quality criteria for genetic association studies in stroke.12 Similar methodological problems are likely to affect existing studies of other candidate genes in stroke. Reliable answers for *APOE* and other candidate genes will only come from studies an order of magnitude larger than those performed to date (ie, with thousands of cases and controls), with appropriate selection of controls and standardized methods for defining subtypes of ischemic and hemorrhagic stroke. This is only likely to be achieved with a multicenter collaborative approach. In the future, statistical methods using marker genotype data may allow the detection and control of confounding attributable to population stratification and selection bias in genetic association studies,22 so avoiding the need for "ideal" control groups, but such methods have not yet been successfully applied in stroke. Case-control studies that are nested within population-based cohort studies are far less prone to control selection bias but need to be extremely large with long follow-up for enough cases to accrue. For example, the UK Biobank study plans to recruit and follow up half a million middle-aged adults. Projections suggest that it will take 5 years for just 1000 stroke cases to occur, suggesting that pooling of data with other similar studies will be necessary to achieve the required sample size for stroke.23 Furthermore, the full potential of such studies will rely on the adequate identification of stroke cases and classification of pathological types and subtypes.12

Addendum

After we completed our systematic review, we have become aware of 2 further relevant studies. In 1, a 3-fold increased odds of previously symptomatic cerebral infarction was found with *APOE* ∈4+ genotypes in an autopsy study (33 cases and 181 controls).[w45] In another, a 2-fold increased odds of lobar ICH was found with *APOE* ∈4+ but not ∈2+

genotypes (107 cases and 205 controls, of whom 67 cases and 131 controls were in a previous report, the results of which were included in our systematic review).[w46] Incorporating the small amounts of additional data from these studies into our meta-analyses would not materially affect our results or conclusions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

C.S. is supported by a Wellcome Trust Clinician Scientist award. N.A.M.G. is supported by CONACyT México. J.K. and C.C. are medical students. We are very grateful to Brenda Thomas for her help with designing the electronic search strategy, and to David Porteous, Charles Warlow, Peter Sandercock and Caroline Jackson for their helpful comments on an earlier draft.

Appendix

Search Strategy in Medline*

1. apolipoproteins/ or apolipoproteins e/
2. ((apolipoprotein$ adj e) or (apoprotein$ adj e) or apo-e or apo e or apoe).tw.
3. ((apolipoprotein$ adj e2) or (apoprotein$ adj e2) or apo-e2 or apo e2 or apoe2).tw.
4. ((apolipoprotein$ adj e3) or (apoprotein$ adj e3) or apo-e3 or apo e3 or apoe3).tw.
5. ((apolipoprotein$ adj e4) or (apoprotein$ adj e4) or apo-e4 or apo e4 or apoe4).tw.
6. ((apolipoprotein$ adj e5) or (apoprotein$ adj e5) or apo-e5 or apo e5 or apoe5).tw.
7. ((apolipoprotein$ adj e7) or (apoprotein$ adj e7) or apo-e7 or apo e7 or apoe7).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular accident/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or exp “intracranial embolism and thrombosis”/ or exp intracranial hemorrhages/ or vasospasm, intracranial/
10. (stroke$ or apoplexy or cerebral vasc$ or cerebrovasc$ or cva$).tw
11. 9 or 10
12. 8 and 11
13. limit 12 to human

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*A similar strategy was designed for Embase

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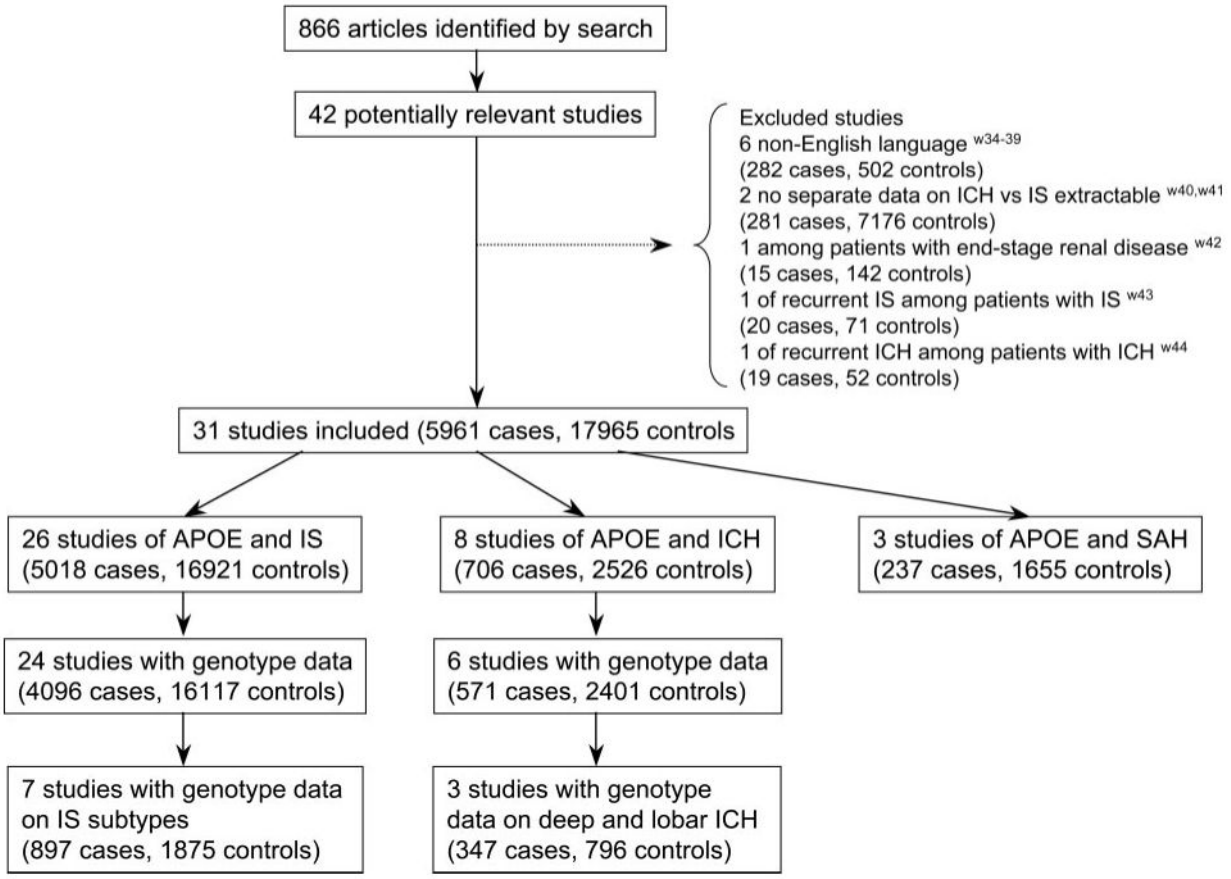

Figure 1.
Flow chart illustrating numbers of studies (and cases and controls) included in the meta-analyses.

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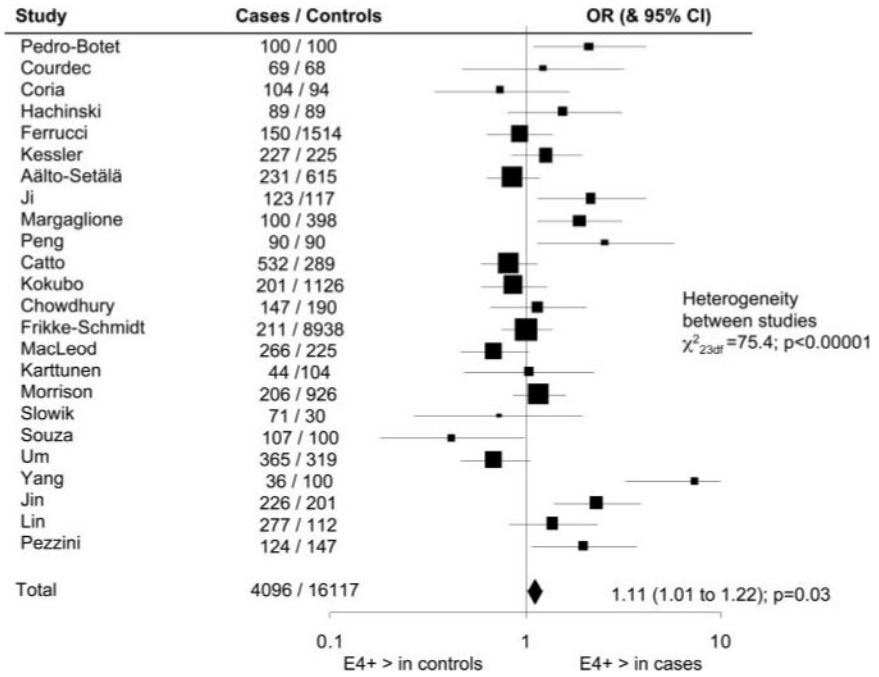

Figure 2.

Meta-analysis of case-control studies of effects of *APOE* ∈4+ genotype on IS. Studies are shown in order of publication date, the earliest first. The OR for each study is shown as a square, the area of which is proportional to its variance, so that larger studies have larger squares. Horizontal lines denote 95% CIs. The summary OR is shown as a diamond, the width of which represents its 95% CI.

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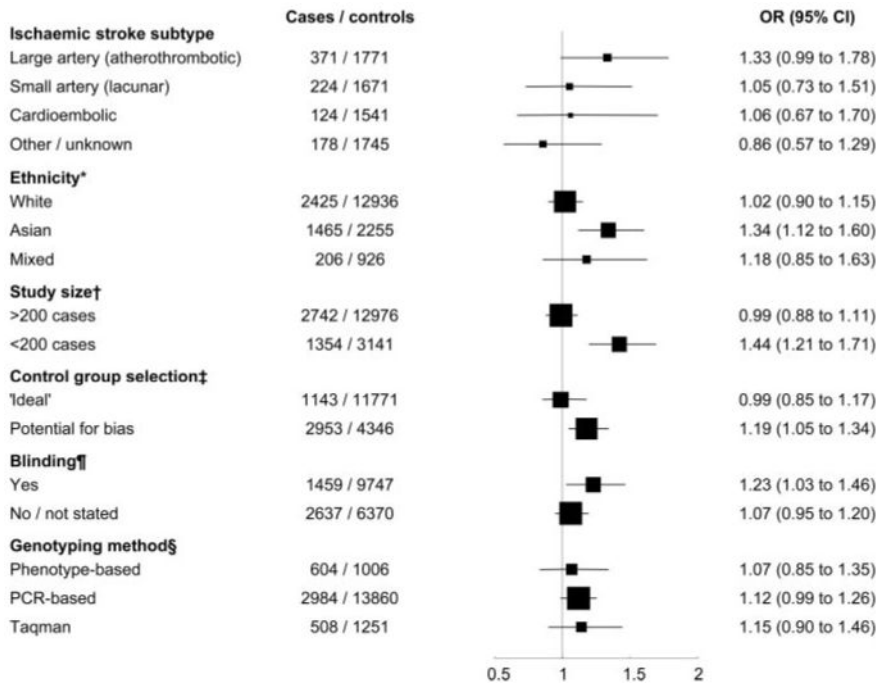

Figure 3.

Meta-analysis of case-control studies of effects of *APOE* ∈4+ genotype on IS-pooled results for various subgroups. The OR for each subgroup is shown as a square for which the area is proportional to its variance, so that larger studies have larger squares. Horizontal lines denote 95% CIs. Formal heterogeneity between IS subtypes was not calculable because of double counting of control groups. *Heterogeneity between 3 groups: $\chi^2$2df=5.6; *P*=0.06. †Heterogeneity between 2 groups: $\chi^2$1df=12.0; *P*=0.0005. ‡Heterogeneity between 2 groups: $\chi^2$1df=2.9; *P*=0.09. ¶Heterogeneity between 2 groups: $\chi^2$1df=1.5; *P*=0.2. §Heterogeneity between 3 groups: $\chi^2$2df=0.1; *P*=0.9.

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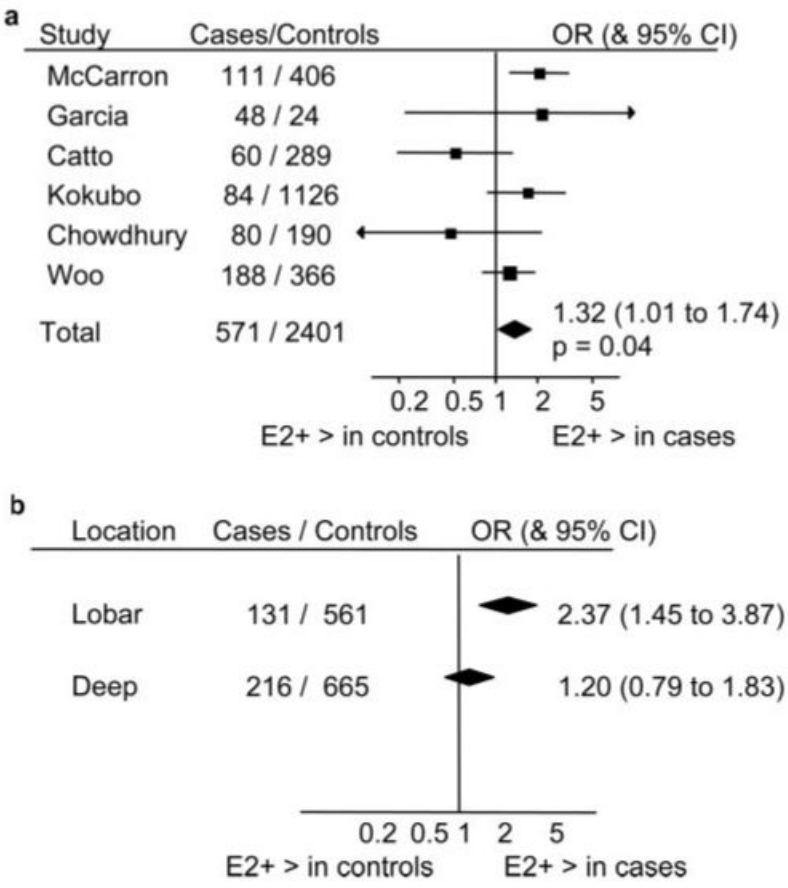

Figure 4.

a, Meta-analysis of case-control studies of effects of *APOE* ∈2+ genotype on ICH. Notation as for Figure 2. Heterogeneity between 6 studies: $\chi^2$5df=9.3; *P*=0.1. b, Meta-analysis of case-control studies of effects of *APOE* ∈2+ genotype on ICH subdivided by location (lobar and deep). The summary OR for each location is shown as a diamond, the width of which represents its 95% CI. Formal heterogeneity between hemorrhage locations not calculable because of double counting of control groups.

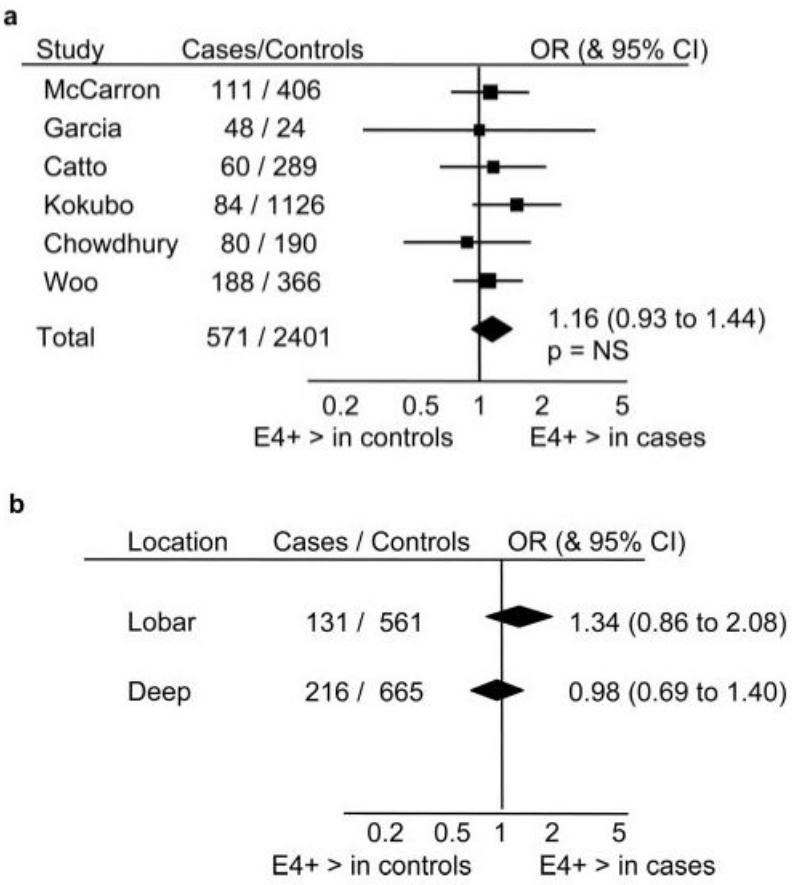

Figure 5.

a, Meta-analysis of case-control studies of effects of *APOE* ∈4+ genotype on ICH. Notation as for Figure 2. Heterogeneity between 6 studies: $\chi^2$5df=1.9; *P*=0.9. b, Metaanalysis of case-control studies of effects of *APOE* ∈4+ genotype on ICH subdivided by location (lobar and deep). Notation as for Figure 4b.

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